incidences of CMV reactivation were reported by other groups using fludarabine in combination with busulphan, melphalan, or low-dose total body irradiation (TBI) (21%-42%).[5,6] The median time of onset of CMV infection was also beyond 45 days in all these studies. The only other regimen associated with a higher and earlier incidence of CMV infection has been a combination of fludarabine and antilymphocyte globulin.[7] Thus, fludarabine used alone, without other antilymphocyte antibodies, does not seem to increase the predisposition to earlier or higher CMV infections. Whether Campath used alone rather than in combination with fludarabine would be associated with a lower incidence of CMV infection remains speculative and is not supported by the existent literature.

I would also like to make a few comments regarding the data presented by Bainton et al.[1] Firstly, the patients receiving BEAM (BCNU, etoposide, cytosine arabinoside, melphalan)–Campath (those not receiving fludarabine) received transplants only for lymphoma/chronic lymphocytic leukemia (CLL) and mostly received matched related grafts (14 of 18). On the other hand, those receiving fludarabine, either as a part of the protocol described by us[2] or in addition to BEAM-Campath, were mostly recipients of unrelated donor grafts (11 of 18) and received transplants mostly for diseases other than lymphoma/CLL (11 of 18). Although the authors mention that there was no difference between related and unrelated donors (UDs), this comparison would be restricted entirely to the fludarabine group, as there were no transplants from unrelated donors in the other group. Thus, to attribute the increased CMV reactivation to fludarabine alone might not be entirely acceptable given the above differences. Given the small sample size and the heterogeneity, the power of a multivariate analysis taking the donor type or underlying diagnosis into account might not be satisfactory either.

Secondly, Bainton et al stated that there was no difference in the incidence of CMV reactivation between patients receiving Campath-1H (alemtuzumab) (15 of 16) and Campath-1G (13 of 20). In fact, the *P* value by Fisher exact test (2-tailed) turns out to be .05. Although the conventional cut-off for significance is .05, it might not be entirely acceptable to ignore a *P* value of .05 and formulate the inferences on a *P* value of .04 (the Fisher exact *P* value for CMV reactivation with and without fludarabine), given the small number of patients. Hence, the statistical interpretation indicates a suggestive trend toward significantly more CMV reactivation in the alemtuzumab group. The effect of alemtuzumab, as we had mentioned, was not only on the incidence of reactivation, but also on the recurrence both before and after 100 days. Late recurrences were correlated with slow recovery of $CD4^+$ T cell counts. And without analyzing these factors and given the above data, it cannot be claimed with certainty that both of these antibodies have a similar effect on CMV reactivation.

Finally, Bainton et al suggested that halving the dose of alemtuzumab might not result in reduction in reactivation of CMV. Indeed, that might be the case and further dose reduction could be necessary, but Bainton et al have used alemtuzumab to day 1 in the protocols other than the one similar to ours. The existing data suggests that the use of alemtuzumab closer to the time of transplant results in longer persistence of the antibody.[8] Thus, only reduction in the dose of alemtuzumab might not suffice, and consideration must be given to its timing in relation to stem cell infusion. Ultimately, how and when to use Campath antibodies in nonmyeloablative conditioning are yet to be perfected, and clinical studies to explore that are ongoing.

Suparno Chakrabarti

Correspondence: Suparno Chakrabarti, Department of Haematology, City Hospital, Dudley Road, Birmingham, B18 7QH, United Kingdom; e-mail: suparno@doctors.org.uk

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To the editor:

Cancer in Fanconi anemia

Three separate and complementary reports recently described the leukemia and solid tumor experience in cohorts of patients with Fanconi anemia (FA).[1-3] Here we examine the similarities and differences of these reports (Table 1) in order to synthesize the most current evidence for physicians and patients.

The literature review (LIT) encompasses 1300 cases reported worldwide from 1927 to 2001.[3] The International Fanconi Anemia Registry (IFAR) includes 754 North American patients ascertained between 1982 and 2001.[2] Our North American Survey (NAS) collected cross-sectional data from 145 patients during 2000.[1] These cohorts are not mutually exclusive, and each study has potential biases. LIT cases are susceptible to publication bias, due to preferential reporting of patients with interesting outcomes. IFAR and NAS cases are subject to selection bias, since they studied volunteers. Some of the data were obtained by unverified self-report, although in the latter 2 studies, neoplasm diagnoses were confirmed objectively.

A strength of the IFAR report is the large number of subjects; a limitation of NAS is its small numbers. All of the cohorts have missing data, hindering some comparisons. Also, IFAR does not distinguish myelodysplastic syndromes (MDS) from leukemia patients, nor solid tumor patients vis-à-vis prior transplantation

Table 1. Summary of FA cohort reports

Cohort	LIT	IFAR	NAS	P*
Reporting period or date	1927-2001	1982-2001	2000	—
Total number of subjects	1301	754	145	—
Male-to-female ratio	1.23	1.05	1.10	ns
Age FA diagnosed, median (range)	7 (0-48)	na	5 (0-45)	<.0002
Deceased %, at time of report	38%	38%	30%	ns
Projected median survival age, years	20	24	30	—
Leukemia, no MDS; number (% total cohort)	116 (9%)	47 (6%)	9 (6%)	<.05
Leukemia, cumulative incidence	na	45% by age 50 (includes MDS)	10% by age 24 (no MDS)	—
MDS, number (% total cohort)	89 (7%)	53 (7%)	23 (16%)	.001
Solid tumor, number (% total cohort)	68 (5%)	67 (9%)	13 (9%)	.003
Solid tumor, cumulative incidence	na	36% by age 50	29% by age 48	—
Liver tumor, number (% total cohort)	37 (3%)	18 (2%)	2 (1%)	ns
Hematopoietic stem cell transplant (% total cohort)	220 (17%)	219 (29%)	44 (30%)	<.0001

ns indicates not statistically significant; na, not available; and —, data in rows could not be subjected to test for significance.
**P* value indicates significance of data at the extremes.

status. Therefore, the impact of MDS and transplantation on hazard rates cannot be assessed. It would be informative for IFAR to separately analyze MDS, acute myeloid leukemia (AML), and solid tumors prior to/after transplantation. Importantly, the competing risk end points differed between IFAR (any adverse outcome) and NAS (first adverse event).

IFAR also defined "hematologic abnormality" as hemoglobin level below 10 g/dL, absolute neutrophil count below 1×10^9/L, or platelet count below 100×10^9/L; LIT and NAS employed the consensus criteria for therapeutic intervention: hemoglobin level below 8 g/dL, absolute neutrophil count below 0.5×10^9/L, or platelet count below 30×10^9/L.[4]

What general conclusions can be drawn by comparing these cohorts? The cumulative incidence of any hematologic finding in FA may be as high as 90%, although bone marrow failure that requires therapy appears to have a cumulative incidence of about 60%. The crude risk of leukemia (exclusive of MDS) is between 5% and 10%, while the cumulative incidence of leukemia (using competing risk analyses) is about 10% by age 25. The crude risk of MDS is about 5%, and the evolution from MDS to leukemia is not inevitable: it was estimated at 9% per year in NAS. It would be valuable to know what this risk was in IFAR.

The crude risk of solid tumors in FA patients who have not received a transplant is 5% to 10%, while the cumulative incidence in the presence of competing risks is about 30% by age 45. Removing competing risks, solid tumor incidence reaches 75% by age 45.[1,3]

The impact of transplantation on the solid tumor hazard rate in FA is not well defined, although some suggest the crude risk reaches 42% by 12 years (3.5% per year) after transplantation.[5] Among IFAR patients, solid tumors developed in 2.7% without and 13% with transplantation. A time-dependent analysis would be more informative, since the crude rates are biased by the short survival of patients receiving transplants. The crude rate for solid tumors in NAS was 0.7% per year versus 2% per year without or with transplantation (rate ratio 2.8; $P = .07$). These data suggest that the risk of solid tumors may be increased by transplantation.

Despite the differences in study design and analysis, the overall impressions are consistent: FA is a condition with very high risks of bone marrow failure, leukemia, and solid tumors. The first adverse event may be determined by each individual's unique combination of FA genotype, cancer susceptibility modifier genes, and environmental risk factors. Future studies are needed to quantify more precisely the individualized risk of each adverse event, elucidate their pathophysiology, and clarify the role of FA genes in the etiology of hematopoietic failure and cancer.

Blanche P. Alter, Mark H. Greene, Isela Velazquez, and Philip S. Rosenberg

Correspondence: Blanche P. Alter, Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, 6120 Executive Blvd, Executive Plaza South 7020, Rockville, MD 20892-7231; e-mail: alterb@mail.nih.gov

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To the editor:

Eosinophils and severe forms of graft-versus-host disease

Basara et al[1] recently reported interesting data on the predictive value of eosinophilia in the evolution to acute graft-versus-host disease (GVHD) in a systematic prospective study of bone marrow smears and biopsies (n = 237). This is in accordance with our previous findings in patients with upper gastrointestinal tract GVHD. In a series of 93 patients, eosinophils were present only when there were histologic signs of GVHD and eosinophil density correlated with GVHD severity.[2] Since few data are available on